Nonequilibrium phase transition in a mesoscoipic biochemical system: From stochastic to nonlinear dynamics and beyond

Hao Ge[1*] and Hong Qian[1,2†]

[1]School of Mathematical Sciences
and Center for Computational Systems Biology
Fudan University, Shanghai 200433, PRC
and
[2]Department of Applied Mathematics
University of Washington, Seattle, WA 98195, USA

May 25, 2009

Abstract

A rigorous mathematical framework for analyzing the chemical master equation (CME) with bistability, based on the theory of large deviation, is proposed. Using a simple phosphorylation-dephosphorylation cycle with feedback as an example, we show that a nonequilibrium steady-state (NESS) phase transition occurs in the system which has all the characteristics of classic equilibrium phase transition: Maxwell construction, discontinuous fraction of phosphorylation as a function of the

*Email: gehao@fudan.edu.cn
†Email: qian@amath.washington.edu

kinase activity, and Lee-Yang's zero for the generating function. The cusp in nonlinear bifurcation theory matches the tricritical point of the phase transition. The mathematical analysis suggests three distinct time scales, and related mathematical descriptions, of (i) molecular signaling, (ii) biochemical network dynamics, and (iii) cellular evolution. The (i) and (iii) are stochastic while (ii) is deterministic.

Microscopic, stochastic molecular fluctuations disappear in the thermodynamic limit in which deterministic nonlinear behavior arises. However, in the mesoscopic world of cellular biology, complex dynamics with multiple time scales makes the meaning of *thermodynamic limit* only relative of one level of description with respect to another. More specifically, we shall show in the present paper that there are three biologically significant time scales, with related levels of mathematical description: (i) stochastic molecular signaling, (ii) deterministic biochemical network dynamics, and finally (iii) stochastic (again!) cellular evolution. In other words, there is stochastic behavior beyond the deterministic dynamics; all three levels are contained in a mesoscopic living system. Current cellular molecular biology chiefly focuses on (i) while increasingly interested in (ii); however, it is the (iii), we believe, that is most relevant to major cellular biological issues such as differentiation, apoptosis, and cancer immunoediting.

Our conclusion is reached through a detailed mathematical analysis of a simple cellular signaling module: a phosphorylation-dephosphorylation cycle (PdPC) with feedback [1]. We use the chemical master equation (CME) as the starting model. In recent years CME has emerged as one of the physiochemical foundations of cellular biochemistry [2]. The theory had begun in 1940 and went through a major development in 1960s and 70s [3]. In particular, the Brussels school has used this theory as a mathematical bases of nonequilibrium steady state (NESS), a term first proposed by Klein [4]. It is now widely accepted that both concepts of CME and NESS are appropriate for studying isothermal, homeostatic cellular biochemistry [5]. The mathematical theory of NESS is an irreversible, but stationary stochastic processes, associated with which the concepts of entropy production and stationary distribution naturally arise [6].

It is generally believed that the deterministic nonlinear dynamics, derived from

the CME in the limit of the reaction system volume $V \to \infty$ according to Kurtz's theory [7], is the macroscopic counterpart of the chemical reaction system [2]. While this is certainly true, here we refine this notion by studying the large-deviation properties of $V \to \infty$, i.e., the thermodynamic limit. We shall show that in the case of a nonlinear dynamical system with multiple dynamic attractors, there is a unique macroscopic thermodynamic state; all the other macroscopic attractors are in fact metastable, with an infinitesimal stationary probability $\propto e^{-\beta V}$ and exponential small exit rate $\propto e^{-\alpha V}$ $(\alpha, \beta > 0)$.

The mathematical theory of large deviation (LDT) [8] is the natural device for understanding the thermodynamic limit of systems with mutlistability, i.e., phase transition(s) [9]. Our result based on the LDT rigorously establishes the stochastic dynamics with bi(multi)-modal distribution as the mesoscopic signature of a nonlinear dynamics with bi(multi)-stability.

We have recently re-examined the nonlinear bistability in the context of biochemical signaling module [10]. In the thermodynamic limit when V tends infinity, there is a phase transition associated with the conventional nonlinear dynamic approach based on the Law of Mass Action, which is the macroscopic limit, in some sense, of the CME [7]. A Maxwell-type construction is an integral part of a complete theory of the CME [10].

In equilibrium phase transition, Lee-Yang theorem for grand canonical partition function is widely considered to be a deep and elegant result [12]. We shall show, non-differentiability of a function $c(\lambda)$ (the NESS counterpart of the free energy function) is the origin of multi-phase behavior, and it is because a zero of $G(\lambda)$ (the NESS counterpart of a partition function) reaches the real axis. Different attempts have been made to generalize the Lee-Yang theory to NESS and to bimodalities in [13].

Large deviation theory, Maxwell construction and first-order phase transition in a NESS. We now consider the same biochemical signaling system in [1, 10] in terms of a one-dimensional CME. Let $p_V(n)$ as its stationary probability for N_V, the random variable representing the activated kinase molecule X; V being the volume of the system.

According to the classic result of LDT [8, 9], especially Sec. 4.5.2 in the text by Dembo and Zeitouni's text, it concludes that if $\frac{N_V}{V}$ satisfies the LDT with a good

"rate function" $\phi(x)$, i.e., $p_V(n) \sim e^{-V\phi(x)}$, $x \geq 0$, then
(a) For each λ, the "free energy function" $c(\lambda) = \lim_{V\to\infty} \frac{1}{V} \log\langle e^{\lambda N_V}\rangle$ exists, and it is finite and nondecreasing. Moreover it satisfies

$$c(\lambda) = \sup_{x\geq 0}\{\lambda x - \phi(x)\}. \tag{1}$$

(b) If $\phi(x)$ is convex, then it is the Fenchel-Legendre transform of $c(\lambda)$, namely,

$$\phi(x) = c^*(x) \triangleq \sup_{\lambda\in\mathcal{R}}\{\lambda x - c(\lambda)\}. \tag{2}$$

(c) If $\phi(x)$ is not convex, then $c^*(x)$ is the affine regularization of $\phi(x)$, i.e. $c^*(\cdot) \leq \phi(\cdot)$, and for any convex rate function f such that $f(\cdot) \leq \phi(\cdot)$ implies $f(\cdot) \leq c^*(\cdot)$.

Consequently, we know that when $\phi(x)$ is bimodal with two local minima, then they are at different heights if and only if the $c(\lambda)$ is differentiable at $\lambda = 0$ according to the well-known Gärtner-Ellis theorem [9], and $\frac{dc(0)}{d\lambda}$ is simply the position of the lower minimum. This implies that the Maxwell construction corresponds to the function $c(\lambda)$ being non-analytic at $\lambda = 0$. Further, if the rate function $\phi(x)$ is analytic, then $c(\lambda)$ is continuous and

$$c(\lambda) = \sup_{\phi'(x)=\lambda} \{\lambda x - \phi(x)\}. \tag{3}$$

If a non-convex $\phi(x)$ has two local minima of $\phi(x)$ with equal height, for sufficiently small $\lambda < 0$, $c(\lambda) = \lambda x - \phi(x)$ for the x near the left minima satisfying $\phi'(x) = \lambda$; and when $\lambda > 0$, also $c(\lambda) = \lambda x - \phi(x)$ for the x near the right minima satisfying $\phi'(x) = \lambda$. Therefore, the left and right derivatives of the function $c(\lambda)$ at $\lambda = 0$ both exist but are equal to the left and right local minima respectively.

If $\phi(x)$ has two local minima x_1 and x_2 with different heights, one can rewrite $\lambda x - \phi(x) = \lambda' x - \psi(x)$ where $\psi(x) = \phi(x) - \lambda^* x$ such that $\psi(x)$ has two minima with equal heights and $\lambda' = \lambda - \lambda^*$. Hence, the nonanalytic point of $c(\lambda)$ moves to λ^*, and also the left and right derivatives at $\lambda = \lambda^*$ both exist and equal to the left and right local minima of $\psi(x)$ respectively. In other words, λ^* is just the slope of the tangent line of $\phi(x)$ with exactly two tangent points. More generally, if the non-convex $\phi(x)$ has k tangent lines with more than one tangent points, then the function $c(\lambda)$ has k non-analytical points, and vise versa. So it is a "higher level" of convexity! [11]

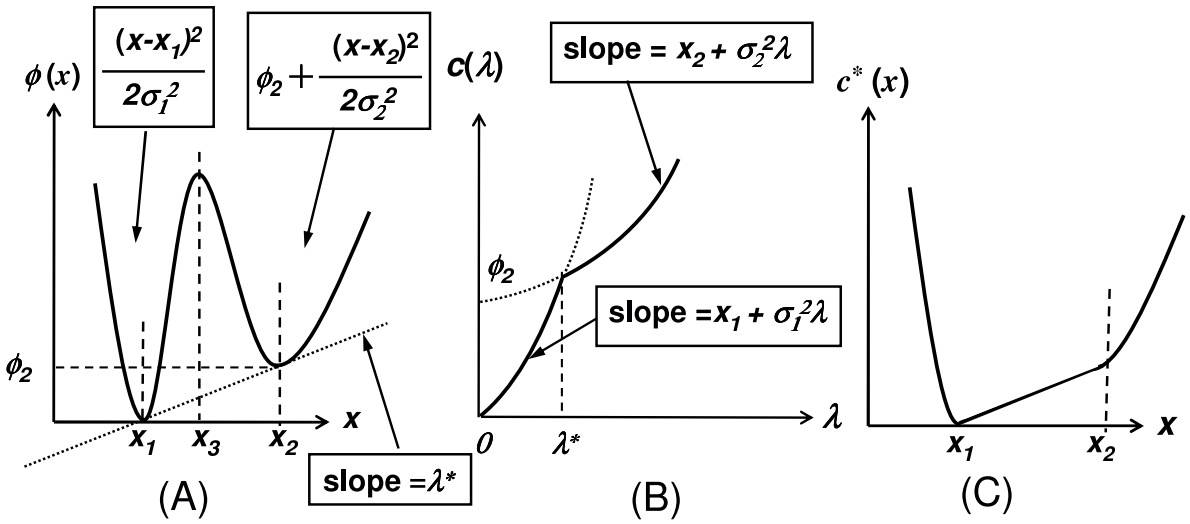

Figure 1: Bimodal, non-convex $\phi(x)$ in (A) gives rise to non-analyticity in the Fenchel-Legendre transform $c(\lambda)$ in (B), the generating function of the N_V in the thermodynamic limit. In equilibiurm statistical mechanics, $c(\lambda)$ is the free energy; hence the non-differentiability at $\lambda = \lambda^*$ indicates first-order phase transition. A quadratic function, with curvature σ^{-2} in (A) gives a quandratic function, with curvature σ^2, in (B). $c^*(x)$ in (C) is the Fenchel-Legendre transform of $c(\lambda)$, also known as the affine regularization of $\phi(x)$.

The above LDT results are summarized in Fig. 1. Fig. 1 shows that, as that in Lee-Yang's theory [12], $c(\lambda)$ is continuous but non-differential at $\lambda = \lambda^*$.

Now let us consider another parameter θ of the system. Let it be a bifurcation parameter in the nonlinear dynamics according to the Law of Mass Action [1]. We have shown in [10] that the stable and unstable fixed points of the nonlinear dynamics correspond precisely with the minima and maxima of the $\phi(x)$, and bistability corresponds to double-wells in $\phi(x)$, and bimodality of $-\phi(x)$.

Here consider the function $(1/V)\log\langle e^{\lambda N_V}\rangle = c_V(\lambda, \theta)$. As V tends to infinity, the limit $c(\lambda, \theta)$ exists, and it is continuous and a non-decreasing function of λ. Furthermore, there is a line in the (λ, θ) plane at which the c is non-differentiable

with respect to λ. The line passes $(0, \theta^*)$ where θ^* is the critical value of Maxwell

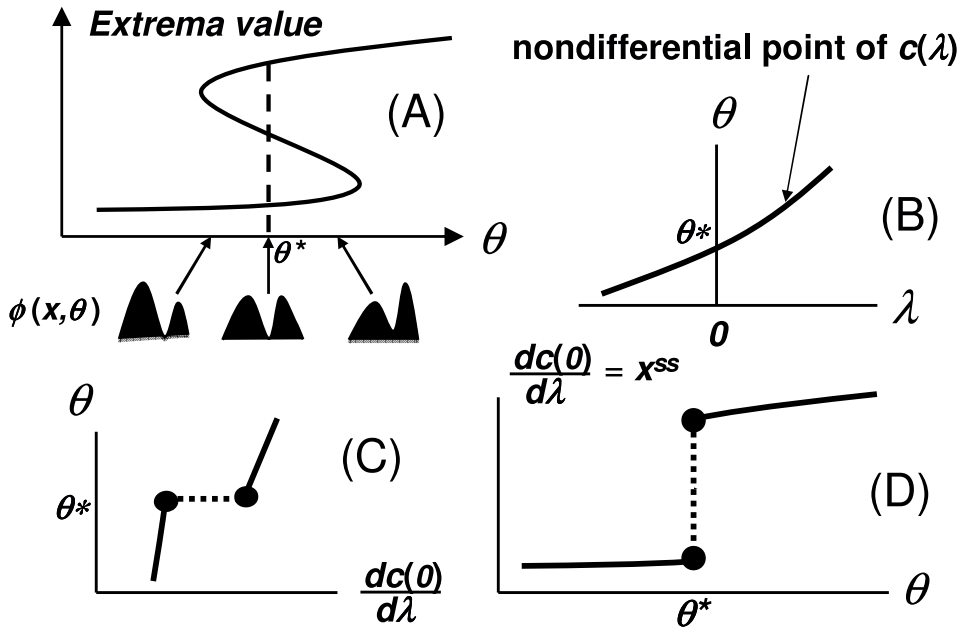

Figure 2: (A) The solid line represents the extrema of the $\phi(x)$, which corresponds to the stable and unstable fixed points of the nonlinear differential equation model. θ is a bifurcation parameter. When $\theta = \theta^*$, the two wells of $\phi(x)$ have equal height. (B) For each value of θ, the double-well $\phi(x)$ yields a non-analytical point $\lambda^*(\theta)$. This line crosses the $\lambda = 0$ when $\theta = \theta^*$. (C) θ as a function of $\frac{dc(0)}{d\lambda}$. (D) $\frac{dc(0)}{d\lambda}$ is in fact the position of the lower minima of $\phi(x)$, which is the mean concentration of X in the system.

In our theory, the derivative at $\lambda = 0$ is particularly meaningful: It is the mean concentration of molecules in the system (property of the generating function). In the thermodynamic limit, the mean and the highest peak position of $e^{-V\phi(x)}$ are the same, the macroscopic value. Thus, we understand that the Maxwell construction implies the mean concentration is not continuous.

Generalizing Lee-Yang's theory. In equilibrium phase transition, according to [12], the non-analyticity in the free energy function $c(\lambda)$ is due to a zero in the partition function $G_V(\lambda) = \langle e^{\lambda N_V} \rangle$ approaching the real axis from the complex plane of λ. Is the non-analyticity in our $c(\lambda)$ also due to the zero of $G(\lambda) = \lim_{V\to\infty} G_V(\lambda)$? This is indeed the case.

Our probability distribution for N_V has a finite support. So the generating function is a finite order polynomial of z, (use $z = e^{\lambda}$). Then consider a region of the complex plane of z, which contains a section of the z axis. According to Theorem 2 in [12] which is a pure mathematical result, the zero of the generating function must be "pinched" onto real z-axis at the non-analytic point of the free energy function $c(\lambda)$ when V tends to infinity. Therefore, our theory generalizes the Lee-Yang theory to nonequilibrium phase transition.

Several previous works have generalized the Lee-Yang theory in nonequilibrium steady states [13] through specific examples. It has been suggested that the bimodal distribution could imply the Lee-Yang theory, but not vice versa. This is consistent with our result.

Cusp catastrophe and tri-critical point in a PdPC with feedback. We consider the simple PdPC with positive feedback which exhibits nonlinear bistability [1]:

$$E + K^* \rightleftharpoons E^* + K^*, \quad K + 2E^* \rightleftharpoons K^*, \quad E^* + P \rightleftharpoons E + P, \tag{4}$$

in which K and K^* are inactive and active forms of a kinase, P is a phosphatase. E^* is the phosphorylated E, a signaling molecule. Usually E^* is functionally active, i.e., "turned-on". Following the previous treatment [1, 10], we assume the reversible binding $K + 2E^* \rightleftharpoons K^*$ is rapid. Hence, the dynamics of the fraction of phosphorylated E, x, satisfies

$$\frac{dx}{dt} = \theta x^2 \left[(1-x) - \epsilon x\right] + \left[\mu(1-x) - x\right] = r(x;\theta,\epsilon), \tag{5}$$

in which the three parameters θ represents the ratio of the activity of the kinase to that of the phosphatase; ϵ represents the ADP to ATP concentration ratio, and μ represents the strength of phosphorolysis. $-k_B T \ln(\mu\epsilon) = \Delta G$ represents the ATP hydrolysis energy. In a living cell, both μ and ϵ are small; hence $\gamma = \frac{1}{\mu\epsilon} \gg 1$.

For large system's volume V, the CME gives the stationary probability $p^{ness}(x) \propto$

$e^{-V\phi(x)}$, where the LDT rate function [10]

$$\phi(x) = \ln(1-x) - x\ln\left[\frac{(1-x)(\theta x^2+\mu)}{x(\theta\epsilon x^2+1)}\right] + 2\sqrt{\frac{\theta}{\mu}}\arctan\left(\sqrt{\frac{\theta}{\mu}}x\right) - \frac{2}{\sqrt{\theta\epsilon}}\arctan\sqrt{\theta\epsilon}x. \tag{6}$$

One can easily check that

$$\frac{d\phi(x)}{dx} = -\ln\frac{(1-x)(\theta x^2+\mu)}{x(\theta\epsilon x^2+1)}, \tag{7}$$

and the extrema match exactly with the roots of $r(x;\theta,\epsilon) = 0$.

The Eq. (5) exhibits saddle-node bifurcations and cusp catastrophe. One obtains the parameter region for the bistability from simultaneously solving $r(z) = 0$ and $\frac{dr(z)}{dz} = 0$:

$$\theta z^2\left[1-(1+\epsilon)z\right] + \left[\mu-(1+\mu)z\right] = 0, \quad \theta\left[2z-3(1+\epsilon)z^2\right] - (1+\mu) = 0. \tag{8}$$

The two equations give the boundary of the region of bistability in (θ,ϵ) space (in terms of z as a parametric curve):

$$\theta = \frac{2(1+\mu)}{z} - \frac{3\mu}{z^2}, \quad \epsilon = \frac{2\mu-(\mu+1)z}{3\mu z - 2(\mu+1)z^2} - 1. \tag{9}$$

Fig. 3A shows the steady states of Eq. (5), x^{ss}, as a function of θ with various ϵ. We see for the range of $\epsilon \leq 1.33$ the system has three fixed points, i.e., bistability. After introducing the Maxwell construction for each and every curve $x^{ss}(\theta)$, we obtain a set of monotonic $x^{ss}(\theta)$. This corresponds to the "PV-isotherm" in the van der Waals theory of phase transition.

According to the cusp catastrope theory [14], there is a region in the $\epsilon-\theta$ plane with three fixed points. The boundary of the region is where the system has exactly two fixed points, i.e., where bifurcation occurs: $\theta_1(\epsilon)$ and $\theta_2(\epsilon)$. One of the most important features of this region is that it has a cusp, at $\theta_{cusp} = \frac{(1+\mu)^2}{3\mu}$, $\epsilon_{cusp} = \frac{1-8\mu}{9\mu}$, when $z_{cusp} = \frac{3\mu}{1+\mu}$, as shown in Fig. 3B.

For a given ϵ, the critical θ^* at which the Maxwell construction is performed satisfies $\theta_1 \leq \theta^* \leq \theta_2$. Thus, the critical line $\theta^*(\epsilon)$ abruptly terminates at the cusp. In equilibrirum phase transition, the cusp is also known as tri-critical point [15].

We also note that bistability implies that the x^{ss} as function of the θ, or ϵ, is not monotonic (it is S-shaped). However, after the Maxwell construction the resulting $x^{ss}(\theta)$ is monotonic in "true" thermodynamic limit! It is precisely the same situation as the PV isotherm in gas-liquid phase transition. The word "true" means one has to wait sufficiently long to allow the jumps back and forth between attractors. The biological significance of monotonicity remained to be elucidated.

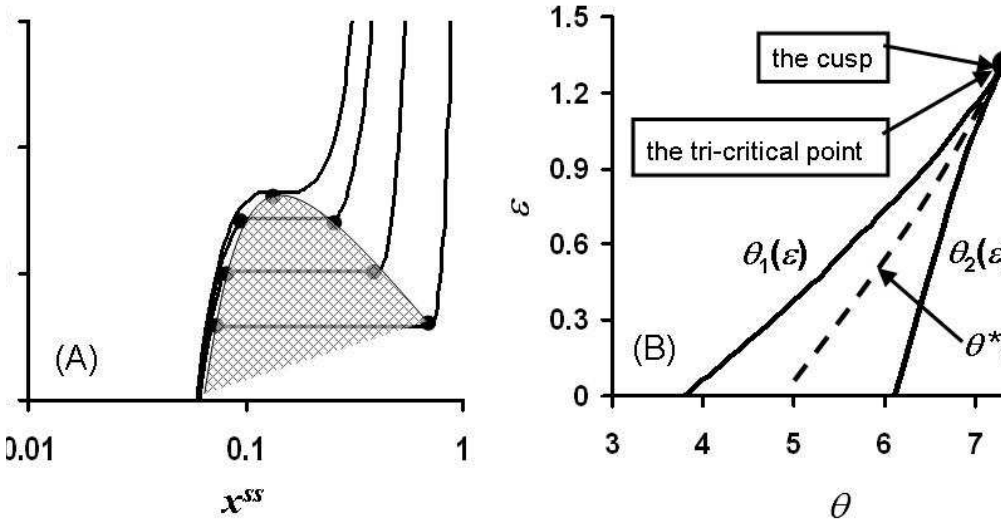

Figure 3: (A) Steady state x^{ss} as functions of θ according to Eq. (5), together with Maxwell constructions under the shaded region. The parameter used $\mu = 0.05$, with $\epsilon = 1.3, 1, 0.5, 0.005$ from top to bottom. (B) The solid lines represent the saddle-node critical points, i.e., the filled circles in (A). They meet at a cusp. The dashed line represents the critical value at which the Maxwell construction is performed. The dashed line terminates at the cusp.

Discussion. The present paper shows that many classical concepts from equilibrium phase transition can be applied to bifurcation problem in nonlinear chemical

dynamics that has a mesoscopic stochastic underline in terms of the CME. From the CME point of view, the LDT treatment we present is a small but significant step beyond the Kurtz theory towards the macroscopic nonlinear dynamics. Analyzing the CME is a much more challenging problem than analyzing the partition function since the former offers a dynamic theory.

The celebrated Maxwell construction is a natural consequence of the general theory we propose, and the well-known Lee-Yang theorem is in fact a special case of it. More importantly, the general theory is applicable to driven systems with nonequilibrium steady state.

On the mathematical side, the general theory provides a framework to study nonlinear bifurcations in terms of mathematical non-analyticity of a certain function, a vision long being hold by some investigators [16]. The large deviation function $\phi(x)$ can be in fact considered as some type of stochastic *landscape* (potential, Lyapunov function in a not rigorous sense) for systems without gradient, nor detailed balance [17].

While the CME as a fundamental theory of studying cellular biochemistry remains to be validated experimentally, it is certainly an acceptable mathematical model for studying mesoscopic complexity and emergent organization, as called by Laughlin et al. [18]. Chemical reactions are marvellous systems for understanding complexity. The present work shows that while Kurtz's theorem is correct, the real limit of V tends infinity is not the solution to the law of mass action, but rather requires a LDT treatment.

The existence of "nice" $\phi(x)$ in the asymptotic form of $e^{-V\phi(x)}$ is not always true for the CME; note that there are chaotic behavior as well involved. If one considers a CME whose corresponding ODE is a 3-dimensional chaotic dynamics with a strange attractor, what will be the stationary distribution in the limit of $V \to \infty$? This problem has been discussed in the past [19]. The general feeling is that $\phi(x)$ is not smooth itself. So one does not have a "nice" $\phi(x)$! For a very "rugged $\phi(x)$", we believe that its Fenchel-Legendre transform $c(\lambda)$ might be a very powerful way to "find the key feature" of the $\phi(x)$. The number of non-differentiable point is definitely much smaller than the number of peaks!

Beyond deterministic dynamics. It is generally believed that when a system's size increases, the stochastic behavior at a mesoscopic level averaged out, and a

deterministic behavior emerges. However, our present analysis clearly show that the emerging deterministic behavior in the CME is a metastable system's dynamics. Beyond that time scale, another "macroscopic" *stochastic* behaviour exists! This multi-attractor stochastic system is a true emerging phenomenon that one can not naively expect from the deterministic dynamics (e.g., based on the relative area of the attractive basins) without detailed stochastic mechanistic modeling. The Maxwell construction is the consequence of the steady state on this "beyond-deterministic-infinite" time scale.

There are three time scales in this mathematical hierarchy of cellular dynamics: A molecular signaling time scale (i.e., the rate constant for molecular interactions), a biochemical network time scale (i.e., the deterministic relaxation times to attractors), and a cellular evolutionary time scale). We believe it is at the last level of stochastic dynamics that is most relevant to major cellular biological issues such as differentiation, apoptosis, and cancer immunoediting.

1 Acknowledgement

HQ thanks Prof. R.M. O'Malley for many helpful discussions. While it is obvious that the problem presented here is intimately related to Laplace integrals and turning-point problems (the star in Fig. 4C), a more comprehensive application of the singular purturbation approach remains to be worked out.

References

[1] J.E. Ferrell and W. Xiong, Chaos, **11**, 227 (2001); H. Qian and T.C. Reluga, Phys. Rev. Lett. **94** 028101 (2005); H. Qian, Ann. Rev. Phys. Chem. **58**, 113 (2007).

[2] M.S. Samoilov and A.P. Arkin, Nat. Biotechnol. **24**, 1235 (2006); D.T. Gillespie, Ann. Rev. Phys. Chem. **58**, 35 (2007); D.A. Beard and H. Qian, *Chemical Biophysics: Quantitative Analysis of Cellular Systems* (Cambridge Univ. Press, London 2008).

[3] M. Delbrück, J. Chem. Phys. **8**, 120 (1940); D.A. McQuarrie, D.A. J. Appl. Prob. **4**, 413 (1967); G. Nicolis and I. Prigogine, *Self-Organization in Nonequilibrium Systems: From Dissipative Structures to Order Through Fluctuations* (Wiley, New York, 1977).

[4] P. Gaspard, J. Chem. Phys. **120**, 8898 (2004); M. Lax, Rev. Mod. Phys. **32**, 25 (1960); M.J. Klein, Phys. Rev. **97**, 1446 (1955).

[5] R. Phillips, J. Kondev, and J. Theriot, *Physical Biology of the Cell* (Garland Science, New York, 2008); E. Karsenti, Nature Rev. Mol. Cell Biol. **9**, 255 (2008); H. Qian, J. Phys. Chem. B **110**, 15063 (2006).

[6] D.-Q. Jiang, M. Qian, M.-P. and Qian, *Mathematical Theory of Nonequilibrium Steady States - On the Frontier of Probability and Dynamical Systems.* (Lect. Notes Math. Vol. 1833, Springer-Verlag, Berlin, 2004); P.G. Bergmann and J.L. Lebowitz, Phys. Rev. **99**, 578 (1955).

[7] T.G. Kurtz, J. Chem. Phys. **57**, 2976 (1972).

[8] A. Dembo and O. Zeitouni, *Large Deviations Techniques and Applications*, 2nd Ed. (Springer-Verlag, New York, 1998)

[9] H. Touchette, arXiv:0804.0327 (2008); R.S. Ellis, *Entropy, Large Deviations, and Statistical Mechanics.* (Springer-Verlag, New York, 1985).

[10] H. Ge and H. Qian, arXiv:0904.2056 (2009); M. Vellela and H. Qian, J. Roy. Soc. Interf. In the press (2009).

[11] We observe that if $\phi(x)$ has three minima, and the middle one is the highest, it seems that the $c(\lambda)$ will be insensitive to the middle minimum! It only depends on the two low ones! However, if the middle one is the lowest, then $c(\lambda)$ will have two non-analytical points.

[12] C.N. Yang and T.D. Lee, Phys. Rev. Lett. **87**, 404 (1952); T.D. Lee and C.N. Yang, Phys. Rev. Lett. **87**, 410 (1952); B.H. Zimm, J. Chem. Phys. **19**, 1019 (1951).

[13] R.A. Blythe and M.R. Evans, Phys. Rev. Lett. **89**, 080601 (2002); Ph. Chomaz, and F. Gulminelli, Physica A, **330**, 451 (2003); H. Touchette, Physica A, **359**, 375 (2005).

[14] R. Thom, *Stabilité Structurelle et Morphogenese* (Intereditions, Paris, 1977); C. Zeeman, in *Structural stability, The Theory of Catastrophies, and Applications in the Sciences,* Vol. 525 of *Lecture Notes in Mathematics,* edited by A. Dold and B. Eckmann (Springer, Berlin, 1976), p. 328

[15] J.A. Gaite, Phys. Rev. A **41**, 5320 (1990).

[16] E.C. Zeeman, Nonlinearity **1**, 115–155 (1988).

[17] R. Graham and H. Haken, Zeit. Physik A **243**, 289–302 (1971); G. Nicolis and R. Lefever, Phys. Lett. A. **62**, 469–471 (1977); J. Ross, K.L.C. Hunt and M.O.Vlad, J. Phys. Chem. A. **106**, 10951–10960 (2002); P. Ao, J. Phys. A. Math. Gen. **37**, L25–L30 (2004).

[18] R.B. Laughlin, D. Pines, J. Schmalian, B.P. Stojkovi and P.G. Wolynes, Proc. Natl. Acad. Sci. U.S.A. **97**, 32 (2000).

[19] G. Hu, Zeit. Physik B **65**, 103–106 (1986); R. Graham and T. Tél, Phys. Rev. Lett. **52**, 9–12 (1984).

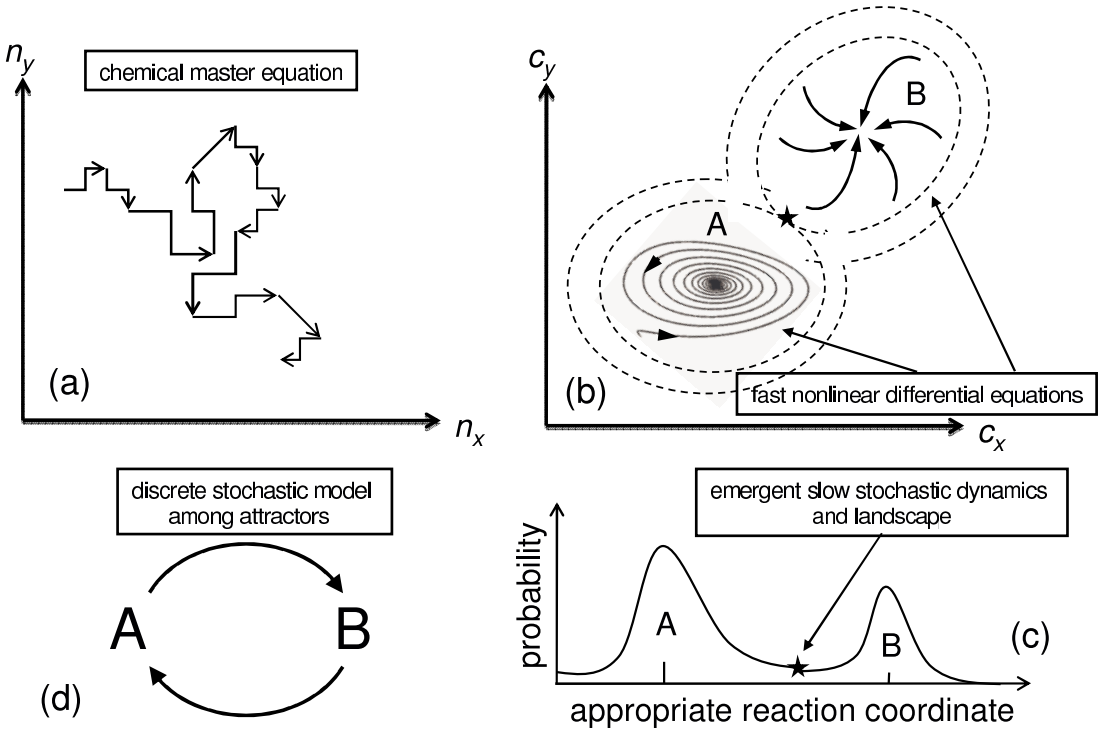

Figure 4: Schematics showing the mathematical hierarchy of cellular dynamics based on the chemical master equation (CME) approach. (a) stochastic dynamics based on the Gillespie algorithm; (b) deterministic dynamics tending to attractors; (c) probabilistic distributions for the two attractors; (d) stochastic dynamics among the attractors. (a), (b) and (c) represent stochastic molecular signaling, deterministic biochemical dynamics, and stochastic cellular evolution, respectively.